Excitable Bursting in the Rat Neurohypophysis

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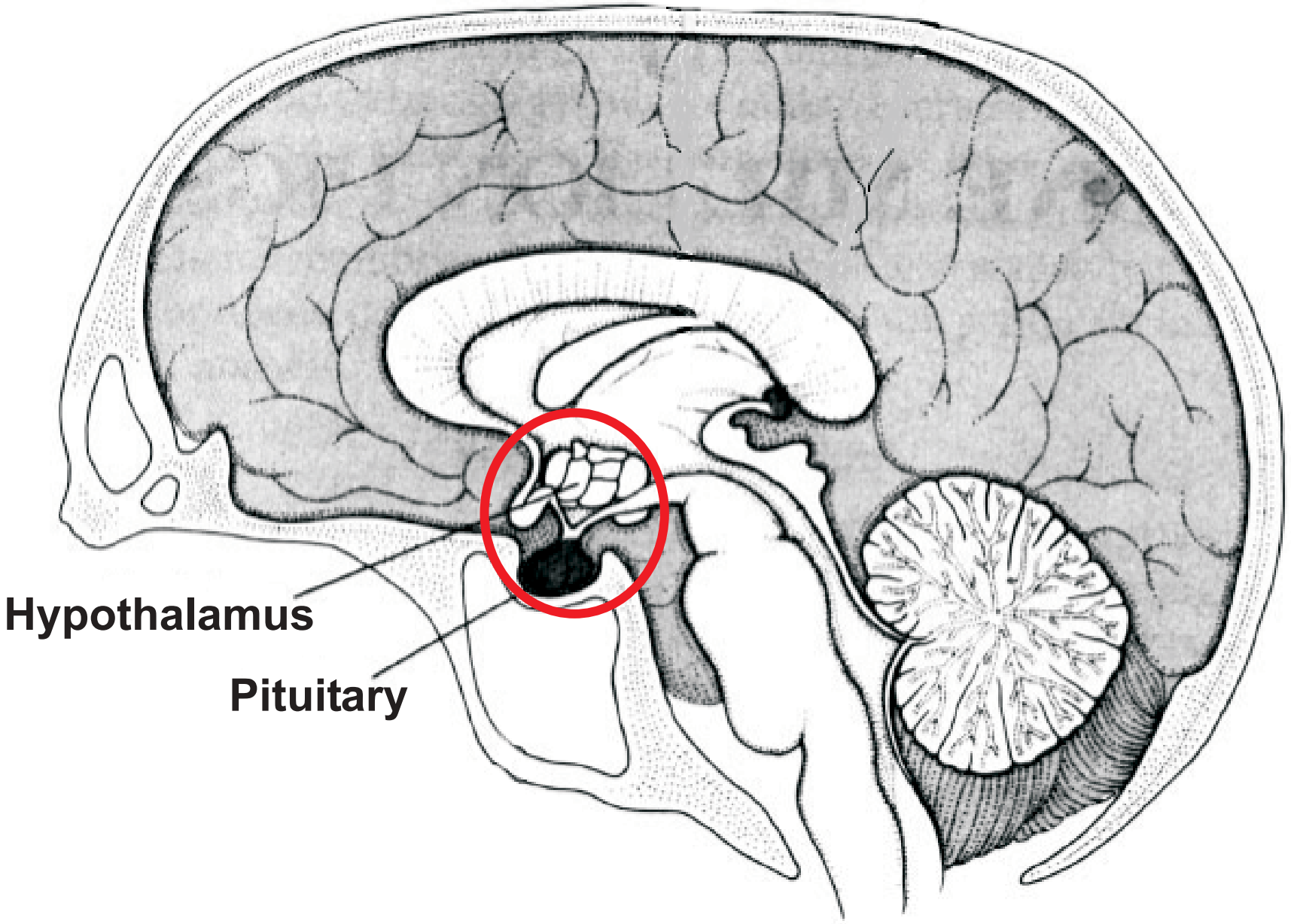
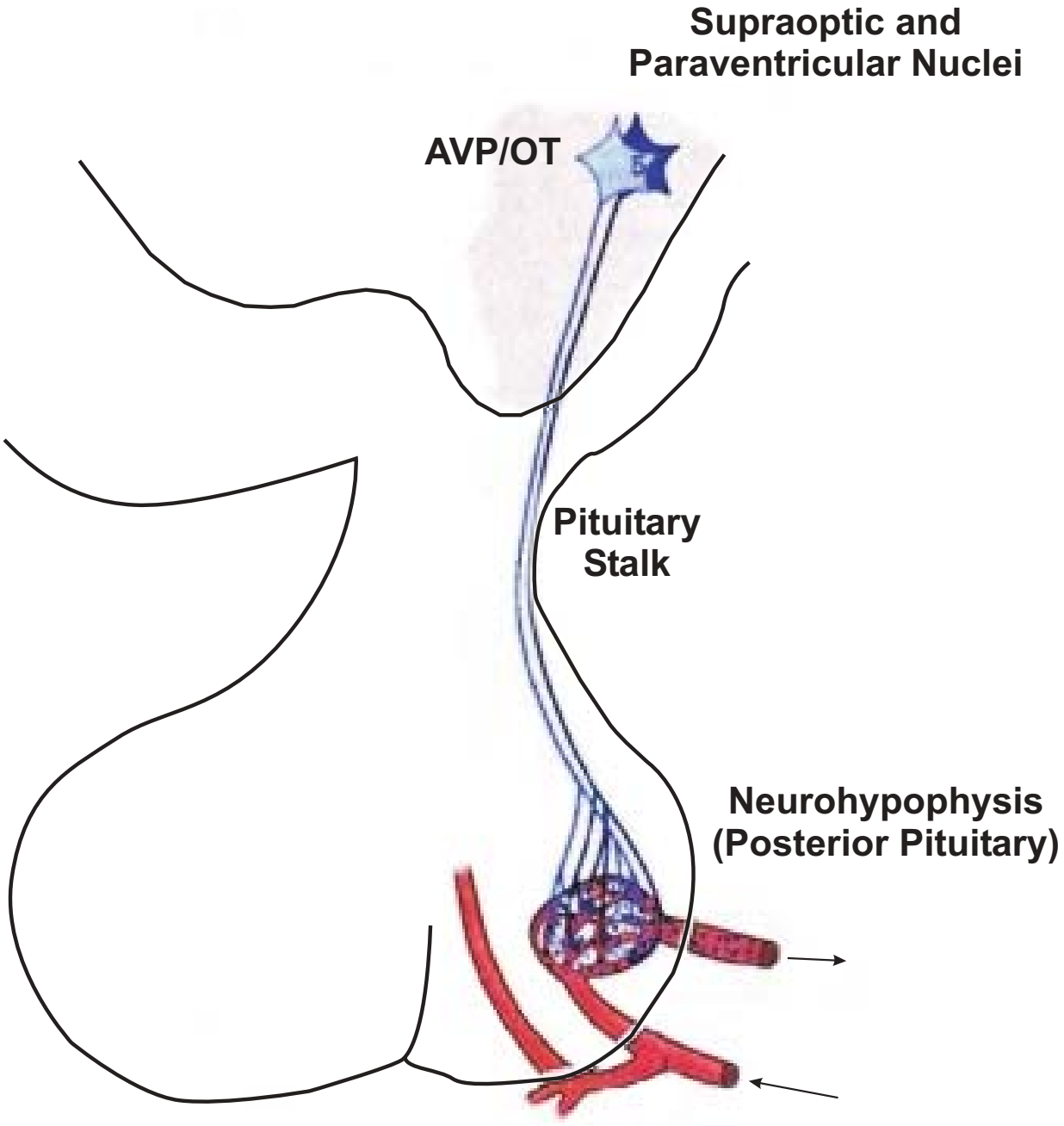
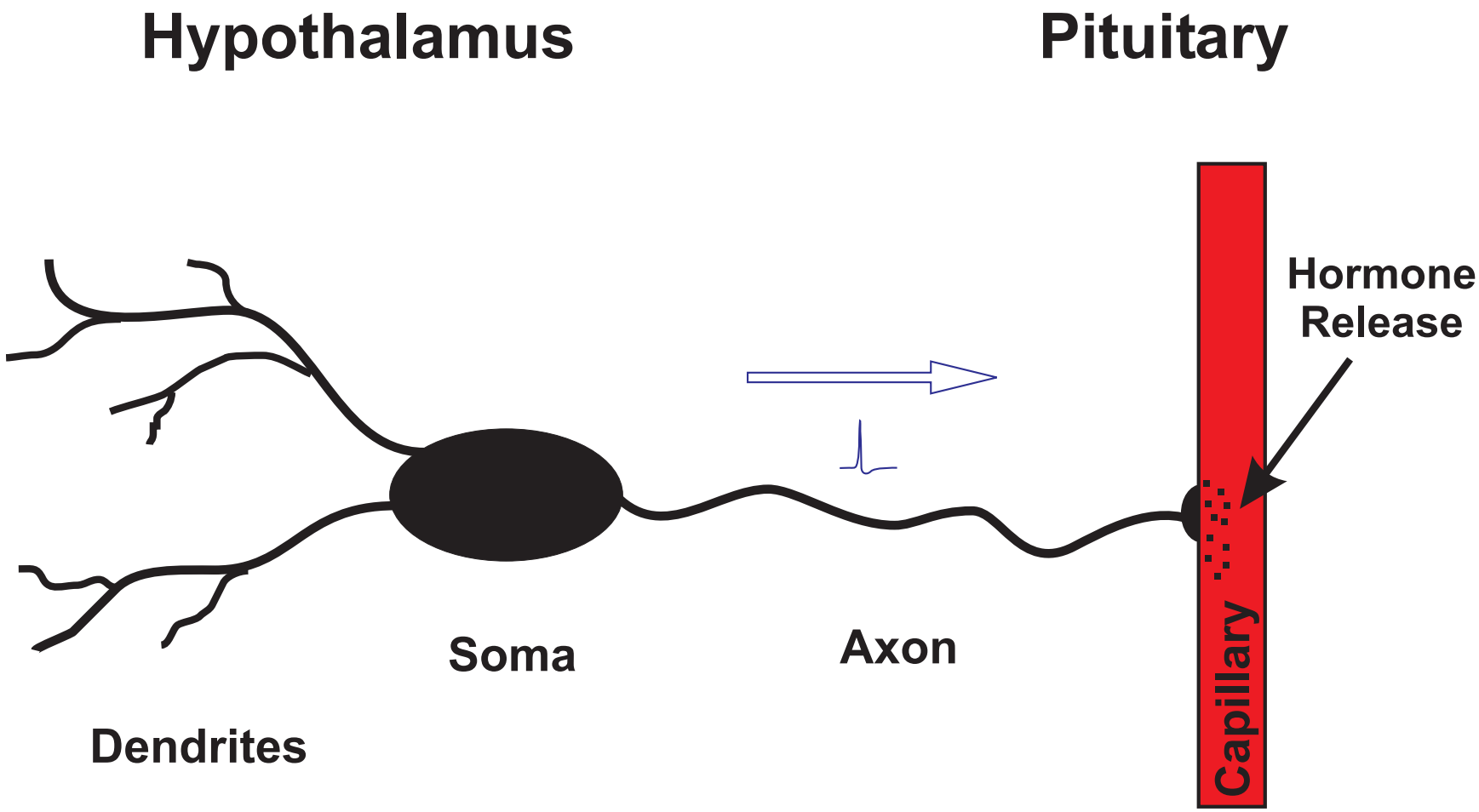
The hormone vasopressin (AVP) regulates:

- blood osmolality (blood concentration)
- blood pressure
- kidney function
- liver function

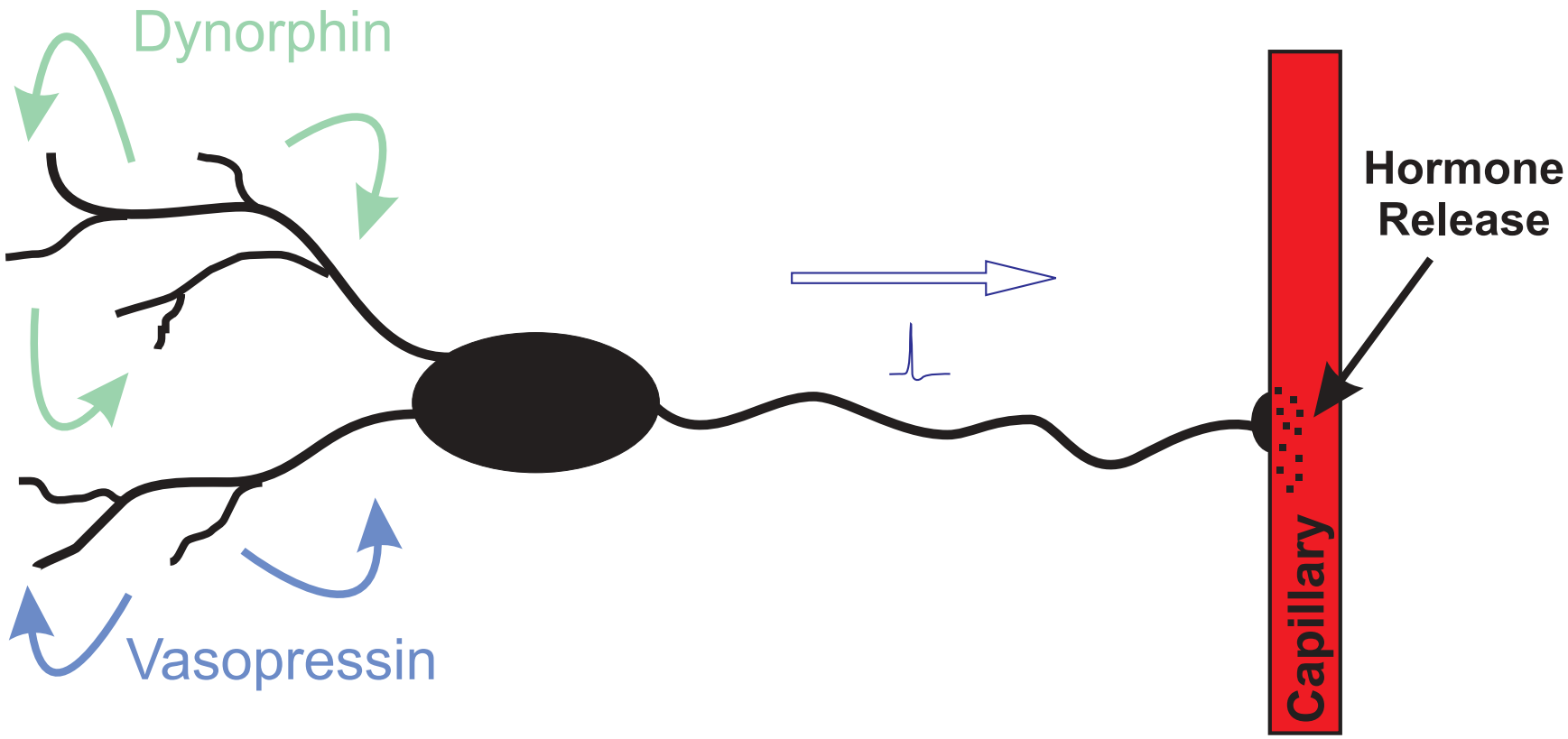
Secretion **increases** during dehydration – mediated by a net depolarization of the cell.


Hypothalamus
Pituitary

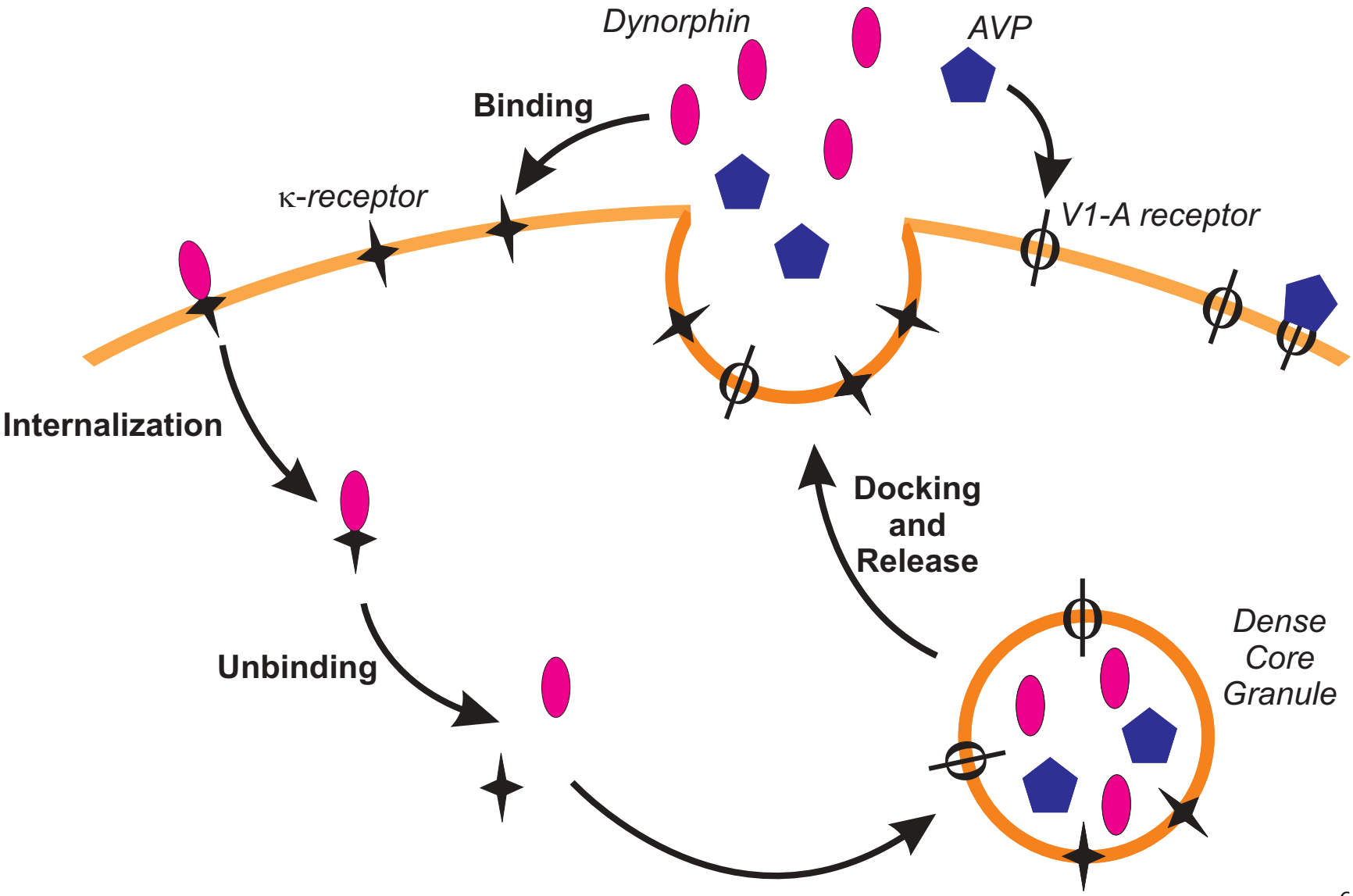

Supraoptic and
Paraventricular Nuclei
AVP/OT
Pituitary
Stalk
Neurohypophysis
(Posterior Pituitary)


Hypothalamus
Pituitary
Hormone Release
Capillary
Soma
Axon
Dendrites

Somato-dendritic secretion of autocrine and paracrine messengers

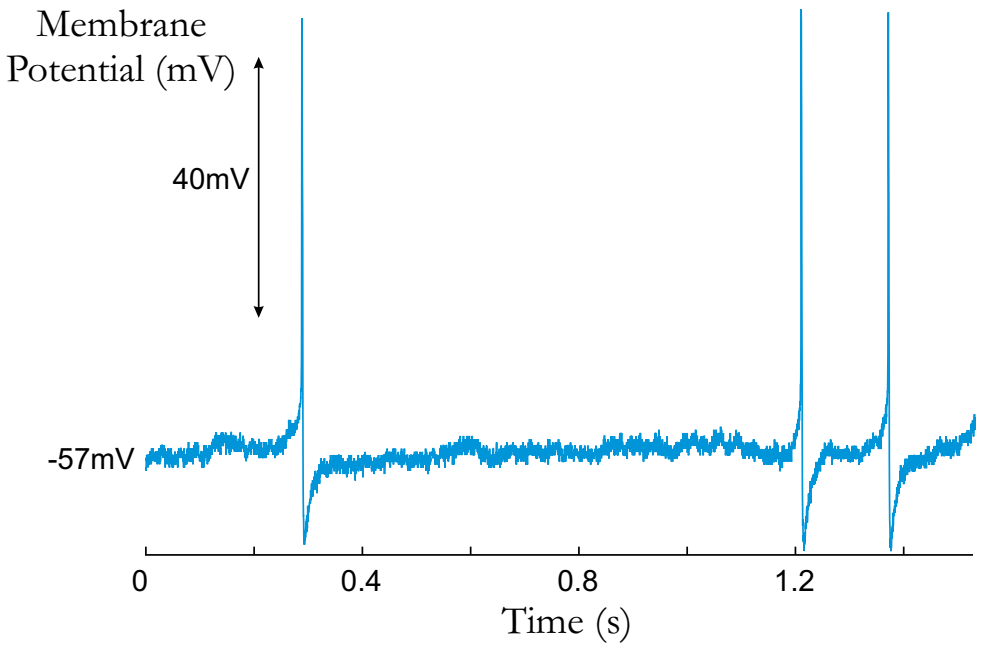


Autoregulatory somato-dendritic release



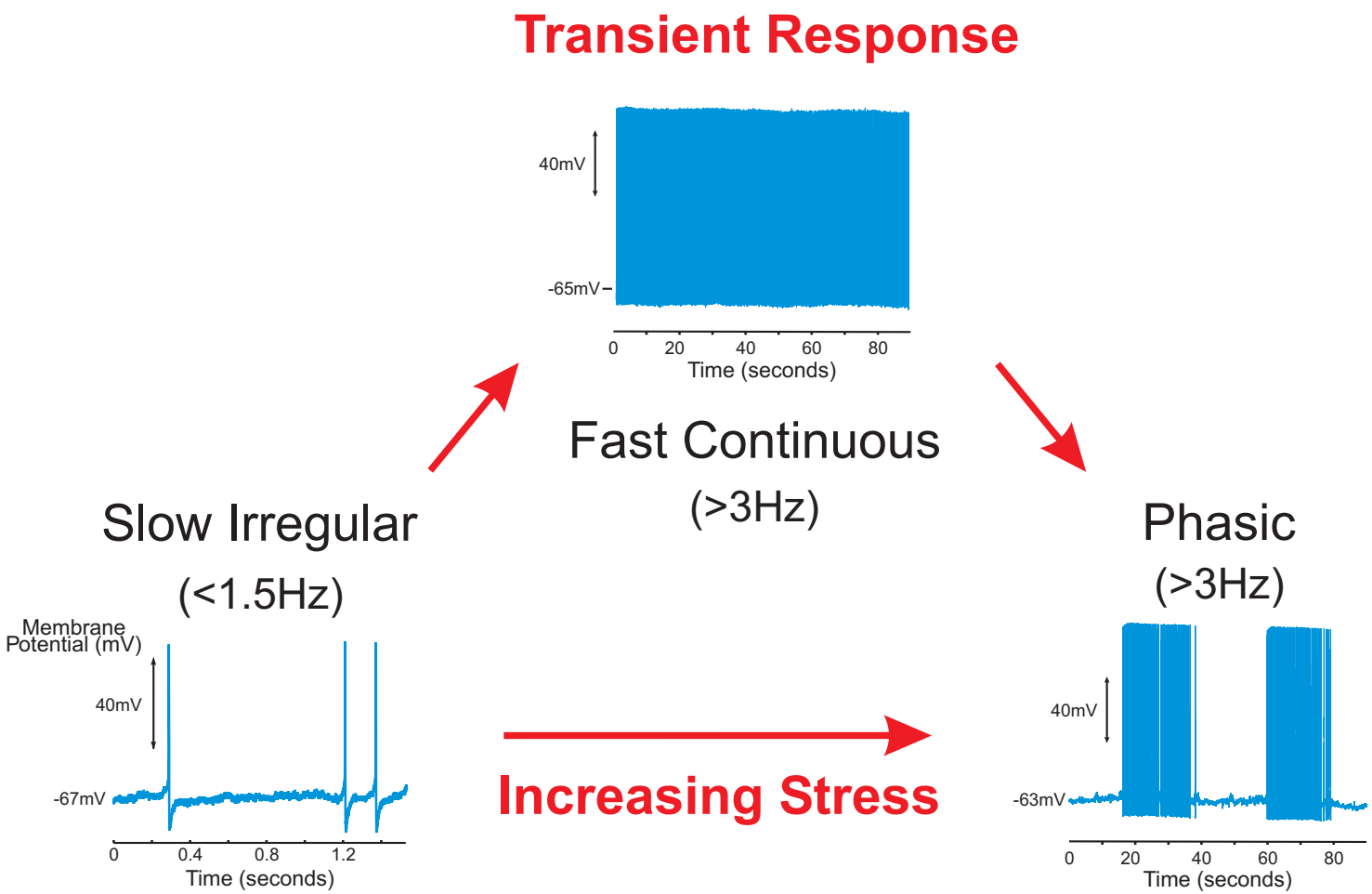
Basal firing is *slow-irregular*

- Poisson distributed spike train
- Spikes evoked by random synaptic input
- Firing rate ≤ 1.5Hz



- Each spike triggers secretion of AVP into the blood

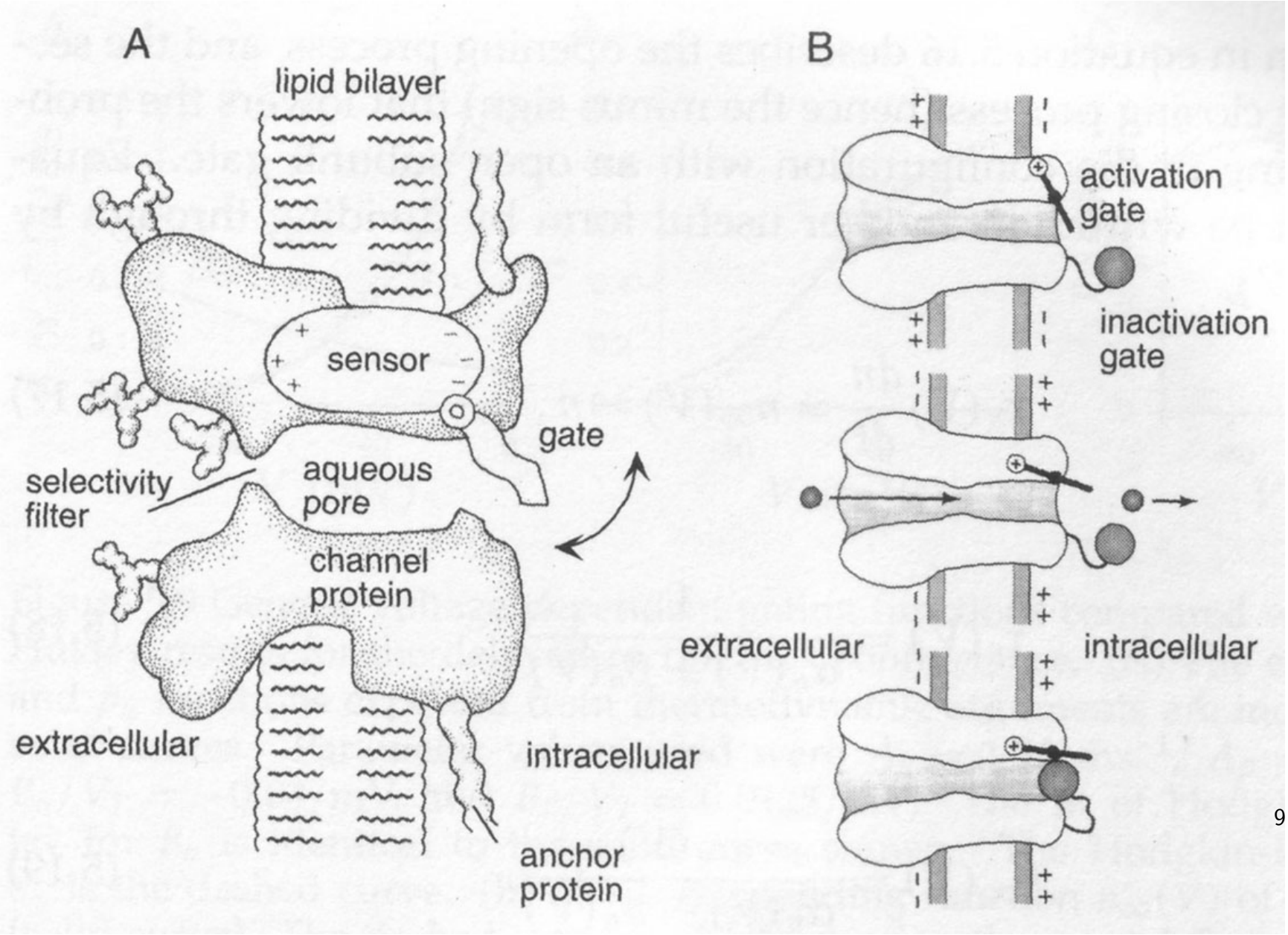
Dehydration alters the firing pattern



- AVP cells switch to a *phasic* pattern
- under extreme stress, AVP cells further switch to *fast-continuous*
- single, non-repeating bursts can be evoked in *slow-irregular* AVP cells

Ionic Currents

Trans-membrane currents mediated by voltage and/or calcium sensitive ion channels

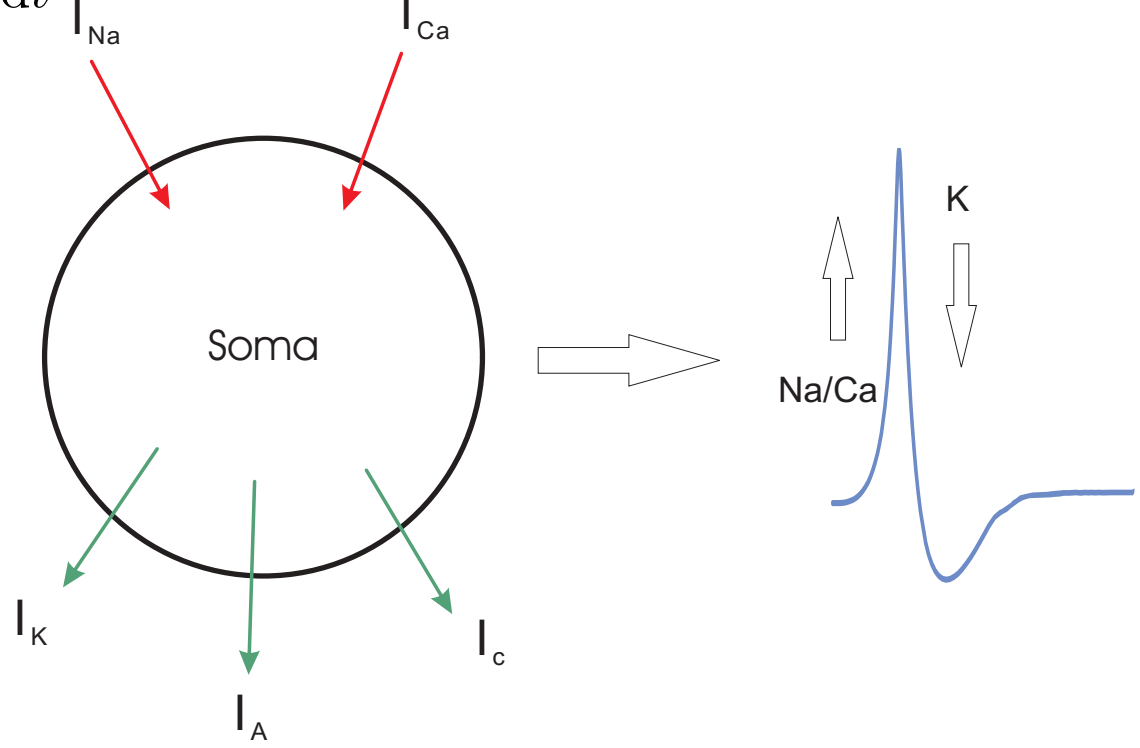


Mathematical Model

Hodgkin-Huxley type system with a simple calcium dynamics

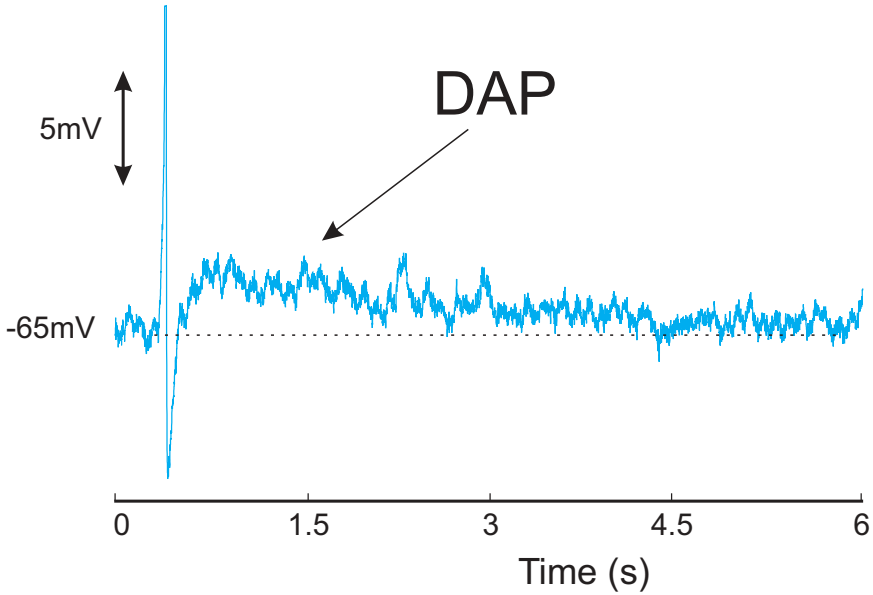
$$-C\frac{\mathrm{d}V}{\mathrm{d}t} = \overbrace{I_{Na} + I_{Ca} + I_A + I_K + I_C}^{\text{Spiking Currents}} + \overbrace{I_{leak}}^{\text{Reset Currents}} + \overbrace{I_{syn}}^{\text{Synaptic Input}}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_i}{\mathrm{d}t} = \underbrace{\alpha I_{Ca}(t)}_{I_{Ca}} - \gamma\left([\mathrm{Ca}^{2+}]_i - [\mathrm{Ca}^{2+}]_{rest}\right)$$

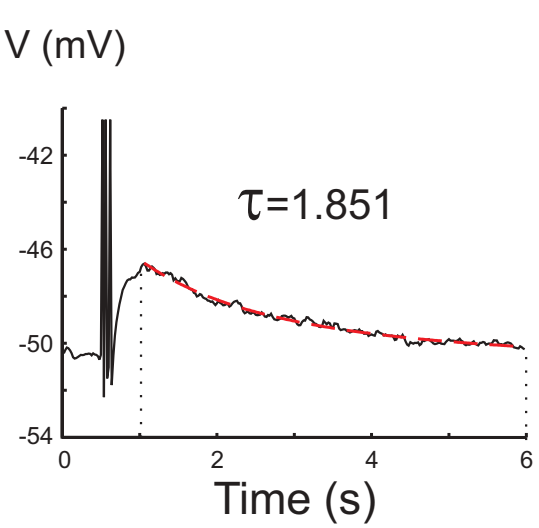


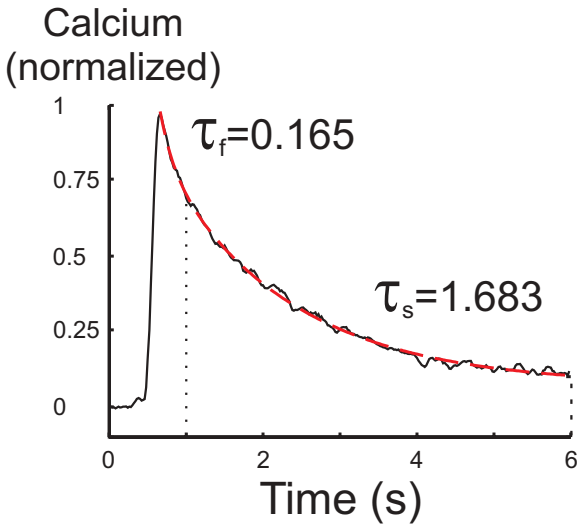
The DAP

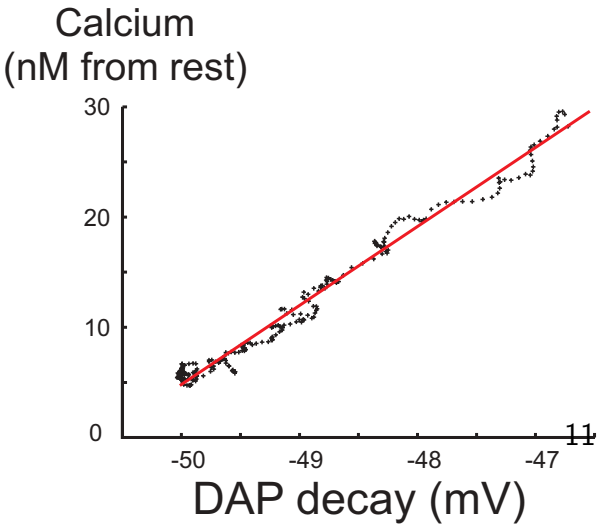
Each evoked spike is followed by a transient depolarization (DAP)



which depends on calcium





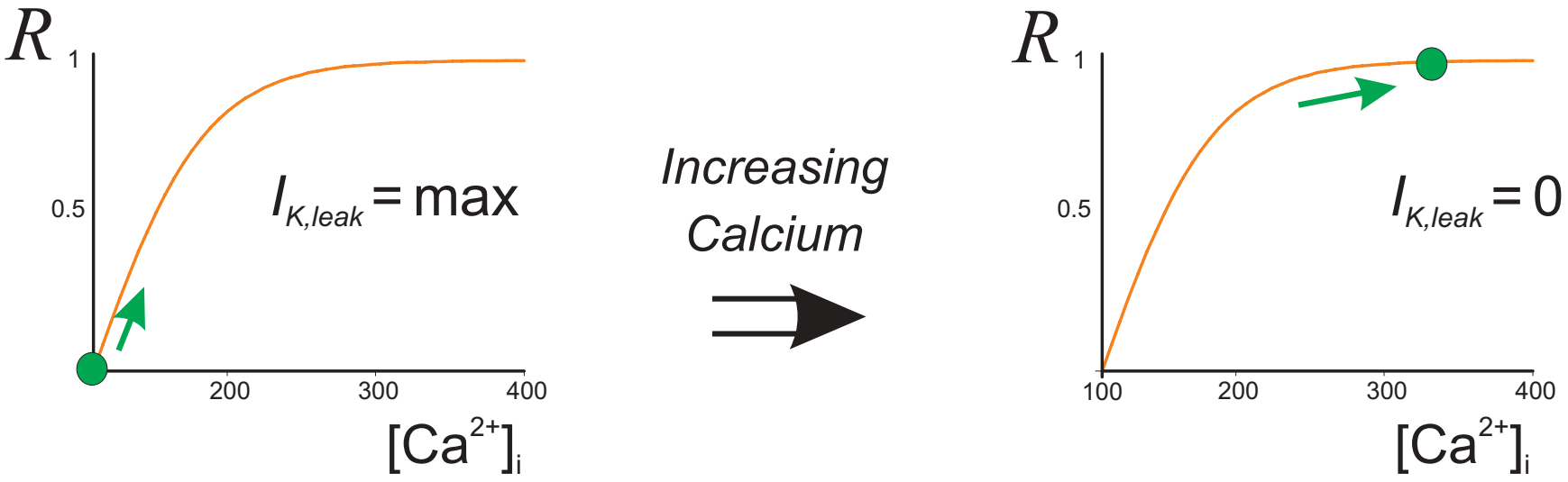


Modelling the DAP

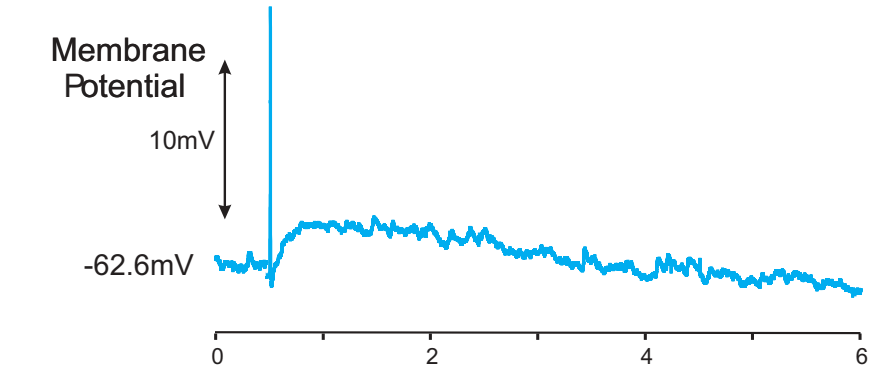
$$I_{leak} = I_{K,leak} + I_{Na,leak}$$

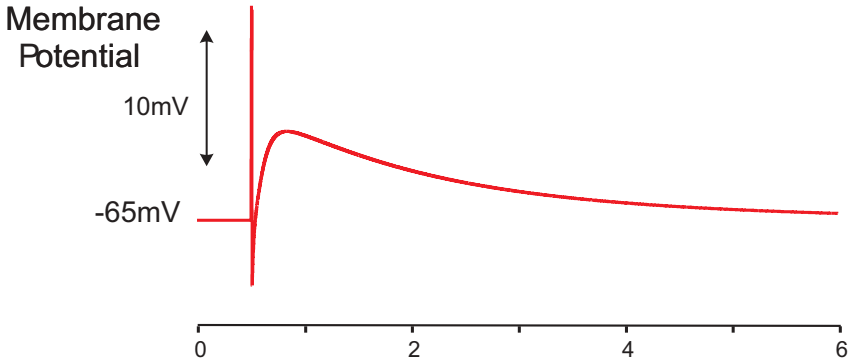
We model (Li and Hatton, 1997) the DAP by a transient (V- and) Ca^{2+}-dependent modulation of a persistent potassium current: $I_{K,leak}$

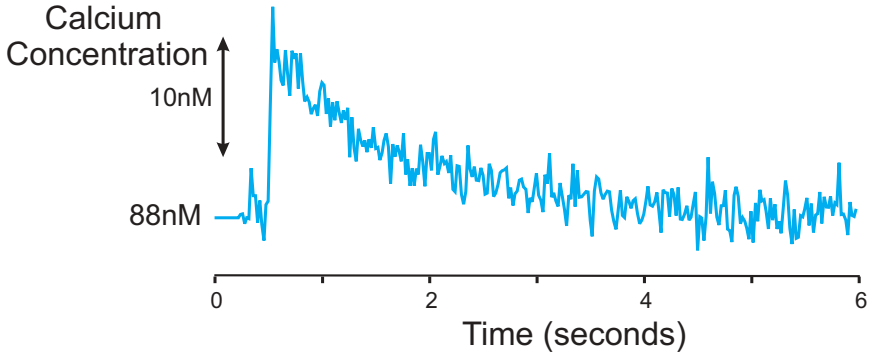
$$I_{K,leak} = (1 - R)\, G_{K,leak}\, (V - E_K)$$

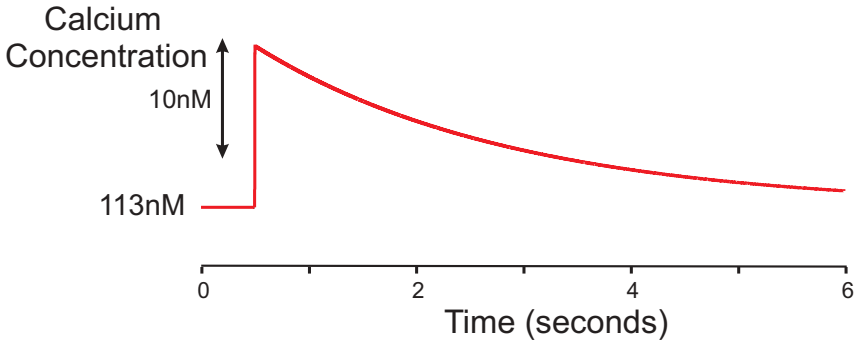


Comparing DAP's from experiment and model

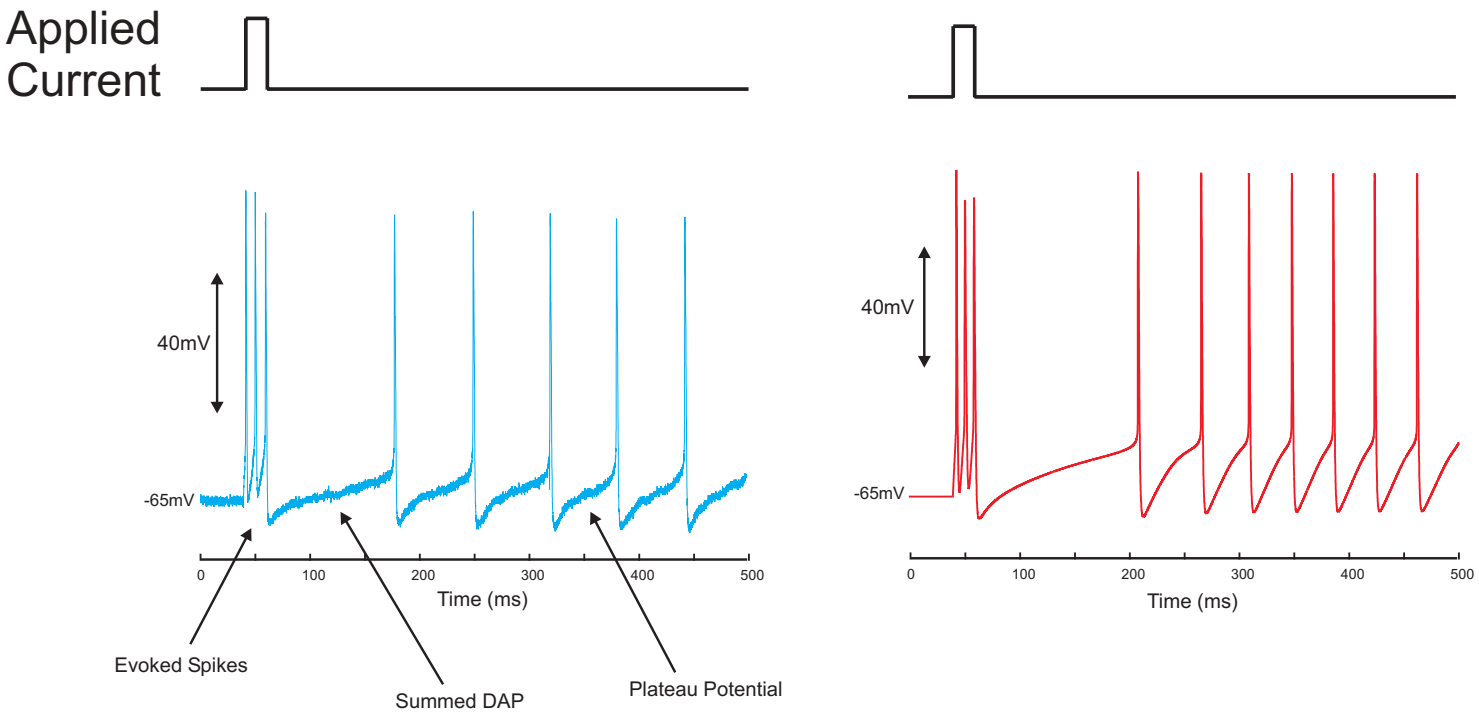




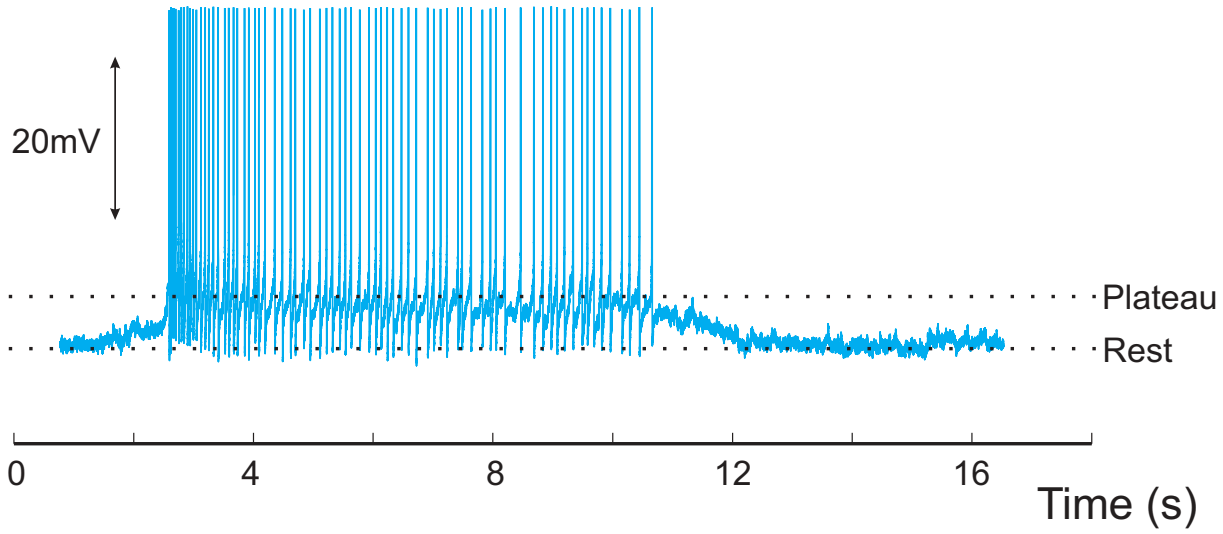


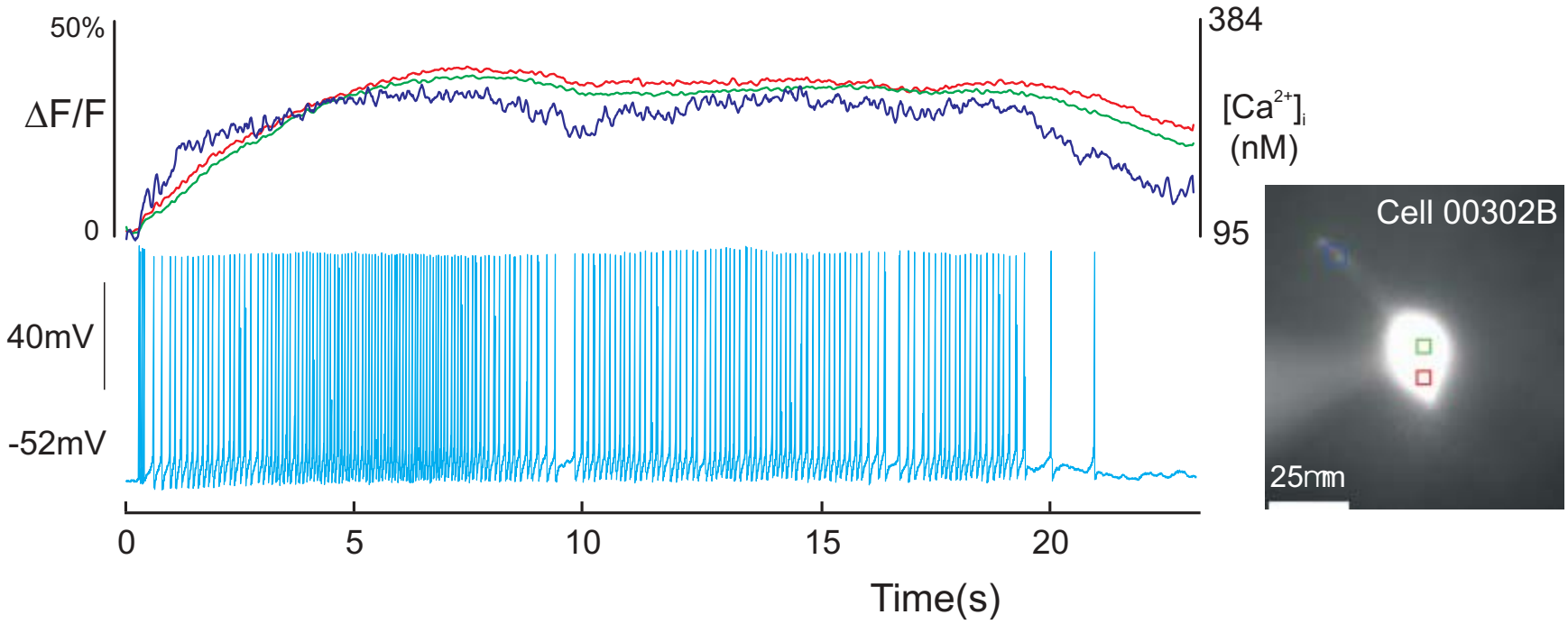


Multiple DAP's summate to a plateau that is above spike threshold:



and such plateaus sustain phasic bursts

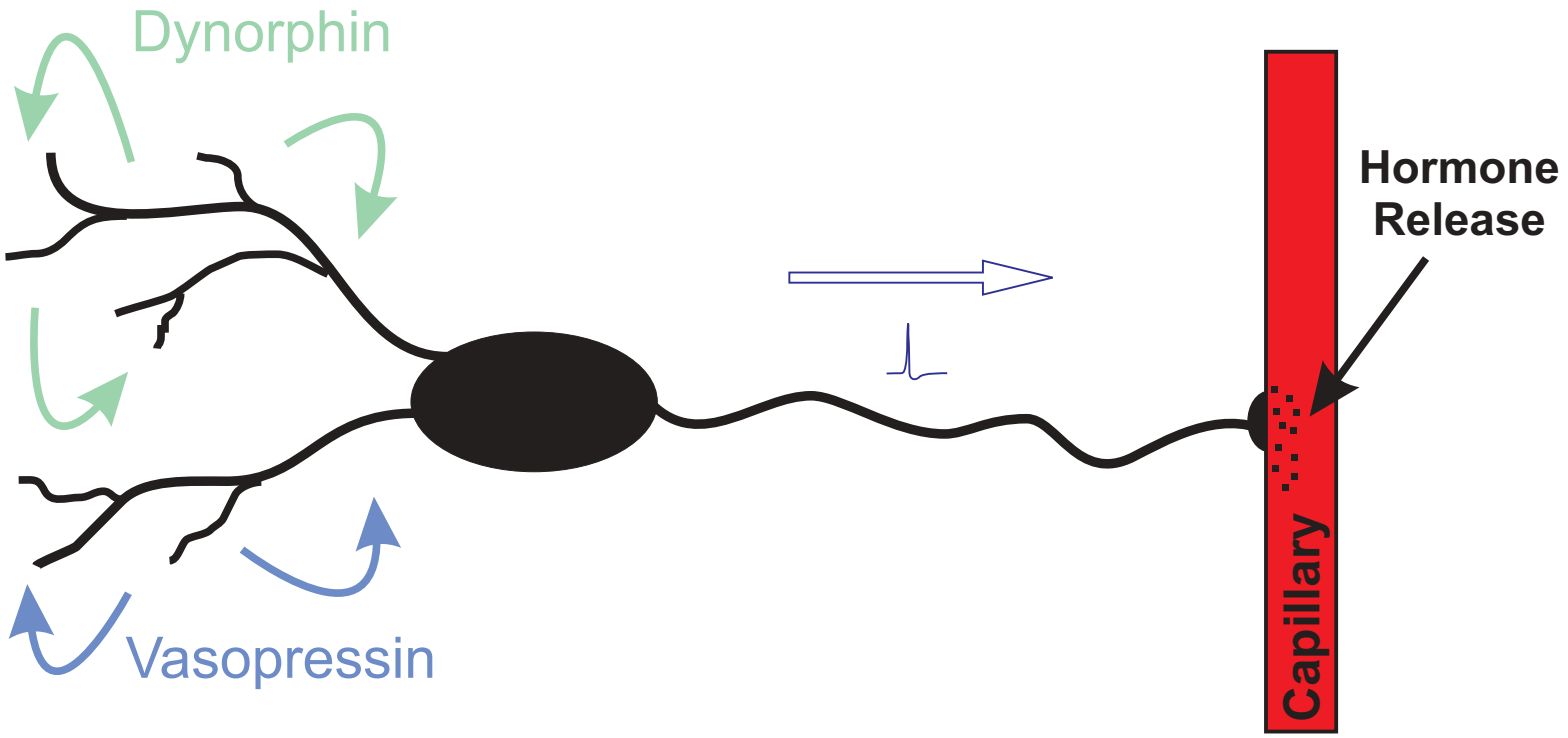




Calcium

- Reaches a plateau early in the burst
- Remains elevated until burst terminates

Question: HOW does burst terminate?



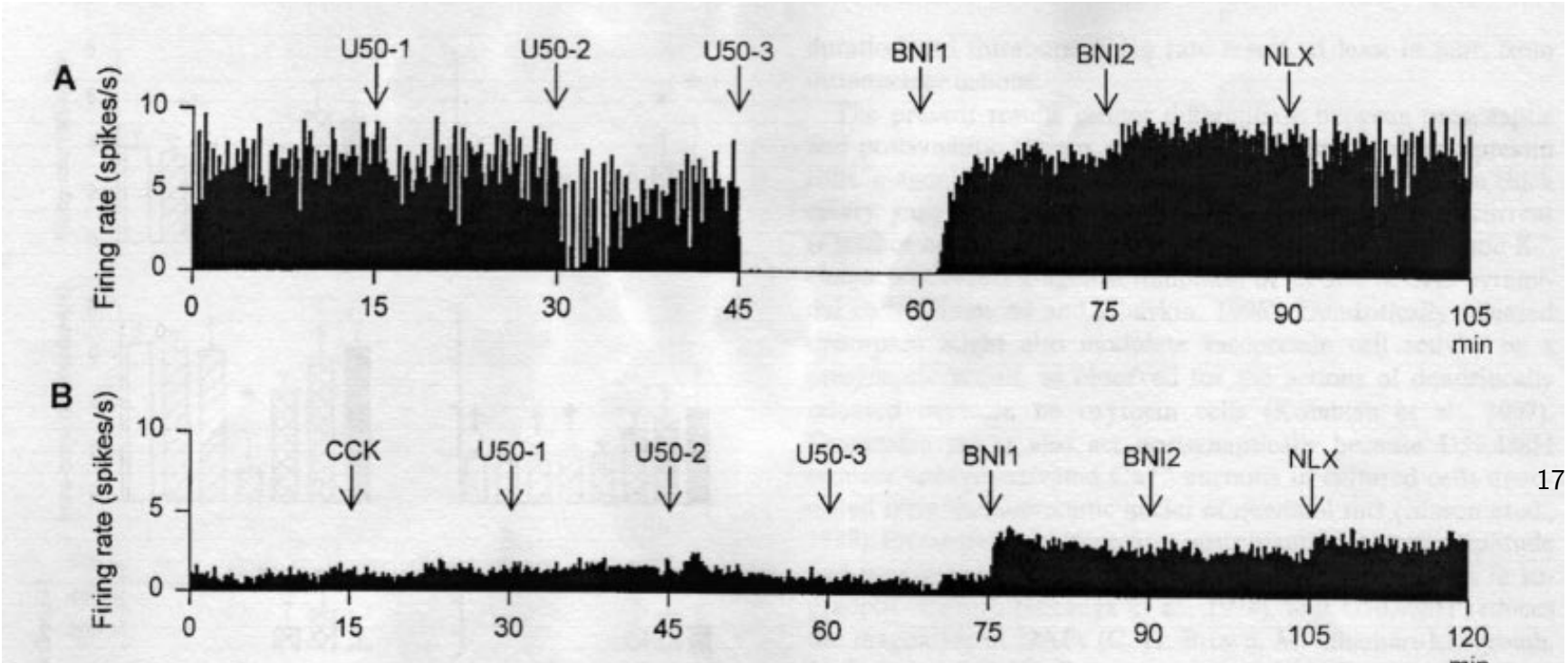
- AVP cells secrete an opioid – dynorphin – from their dendrites
- Dynorphin inhibits AVP cell activity
- Propose that effects of dynorphin increase during active phase and clear during silent phase

Dynorphin agonists (U50-3):

- Inhibit the DAP
- Prevent bursting (Brown *et al.*, 1999)

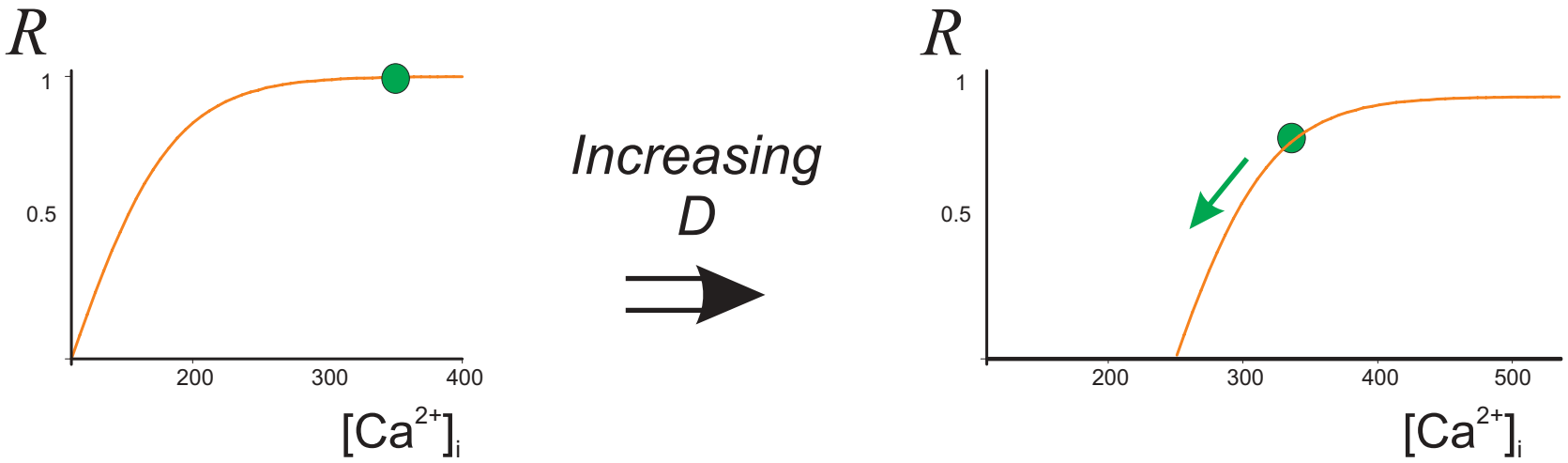
Dynorphin antagonists (BNI):

- Prolong durst duration (Brown, 1999)

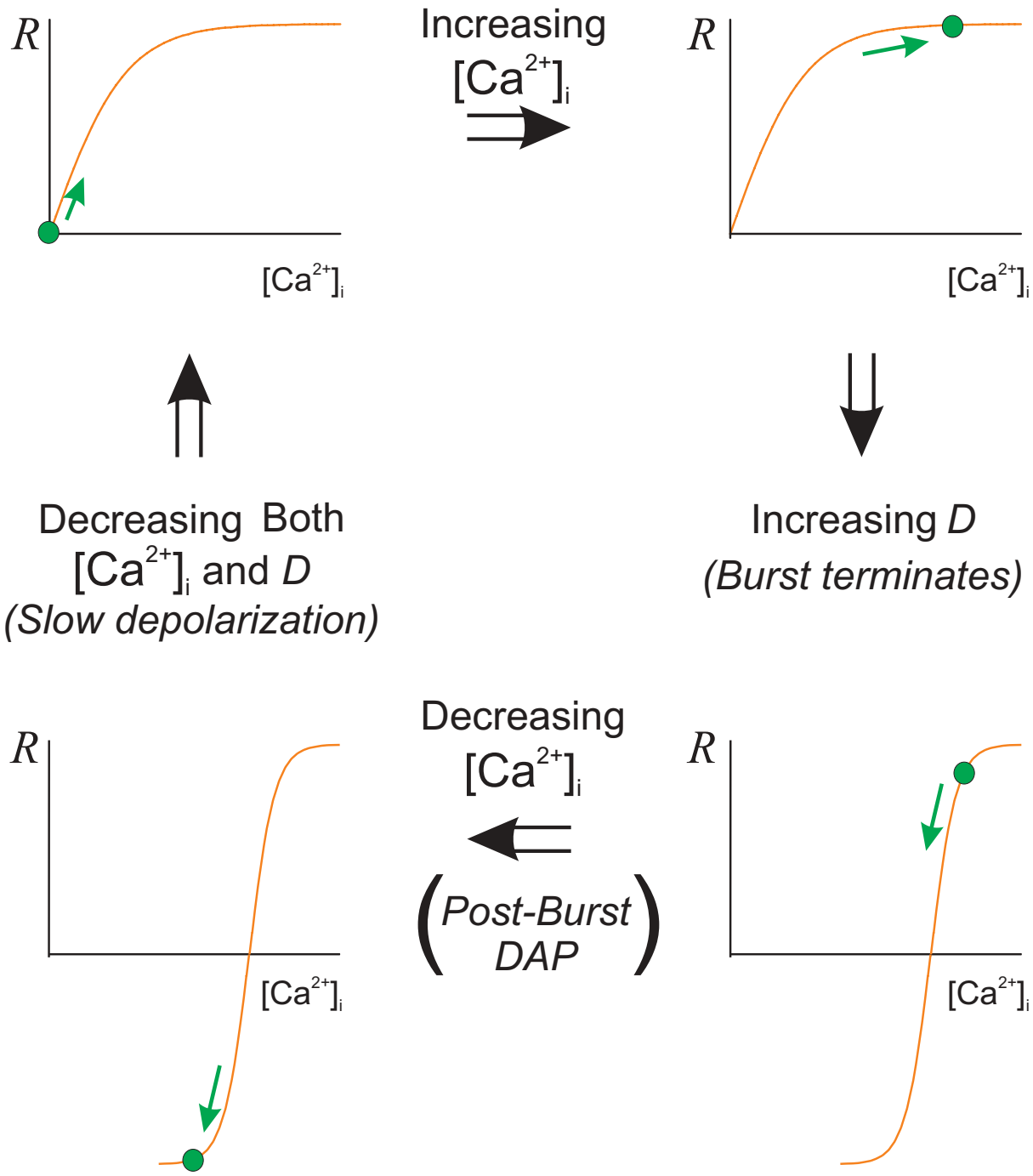


HOW does dynorphin act?

- **We propose** that dynorphin shifts the half-activation of R to higher Ca^{2+} concentrations



- **Thus** raising the plateau threshold while leaving $[\mathrm{Ca}^{2+}]_i$ unchanged
- **Eventually** plateau can no longer support spiking and cell falls silent – burst terminates


R
[Ca2+]i
Increasing
[Ca2+]i
R
[Ca2+]i
Decreasing Both
[Ca2+]i and D
(Slow depolarization)
Increasing D
(Burst terminates)
R
[Ca2+]i
Decreasing
[Ca2+]i
(Post-Burst
DAP)
R
[Ca2+]i

Dynamics of dynorphin and the κ-receptor

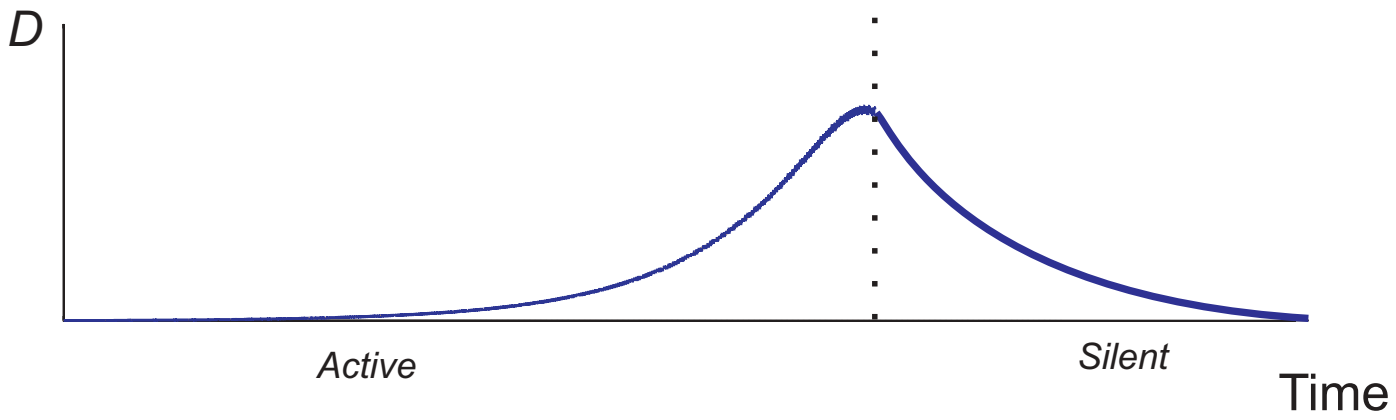
- D is augmented by Δ when the cell fires the i^{th} spike (say at time T_i)
- D decays exponentially between spikes

$$\frac{\mathrm{d}}{\mathrm{d}t}D = \Delta\delta(t - T_i) - \frac{1}{\tau_D}D \qquad \Delta = \text{constant}$$

Upregulation of the κ-receptor

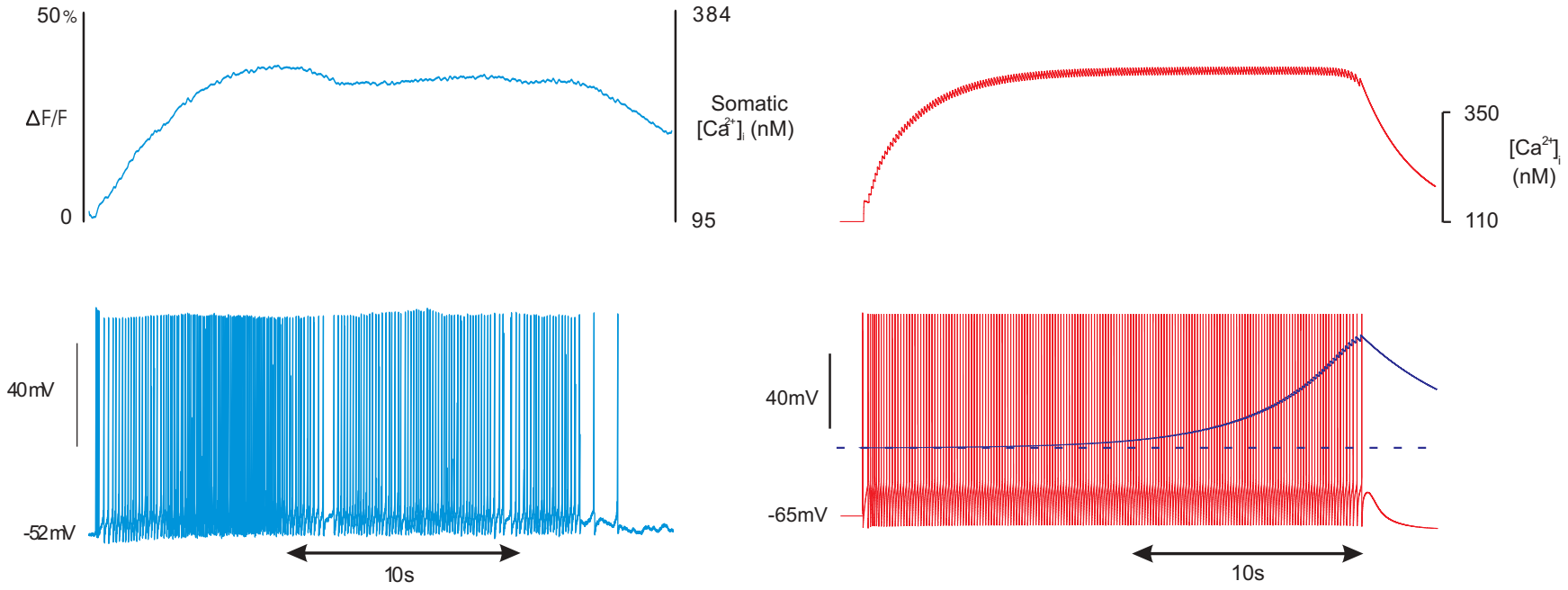
Propose that Δ increases as a function of D

$$\frac{\mathrm{d}}{\mathrm{d}t}D = \Delta\delta(t - T_i) - \frac{1}{\tau_D}D \qquad \Delta(D) = \Delta_0 + \epsilon D$$



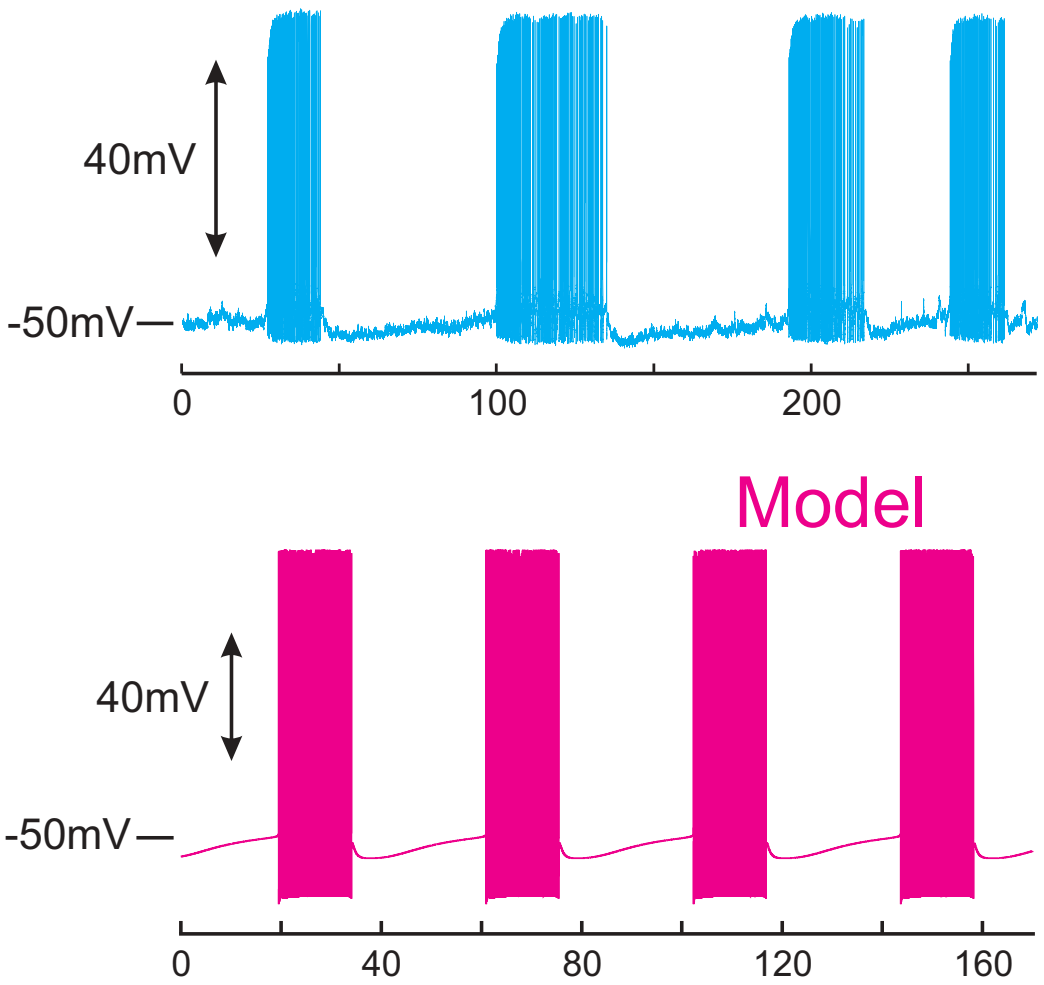
- **Interpretation:** dynorphin upregulates κ-receptor density

Comparisons between real and model bursts



If cell depolarized far enough...

...phasic activity

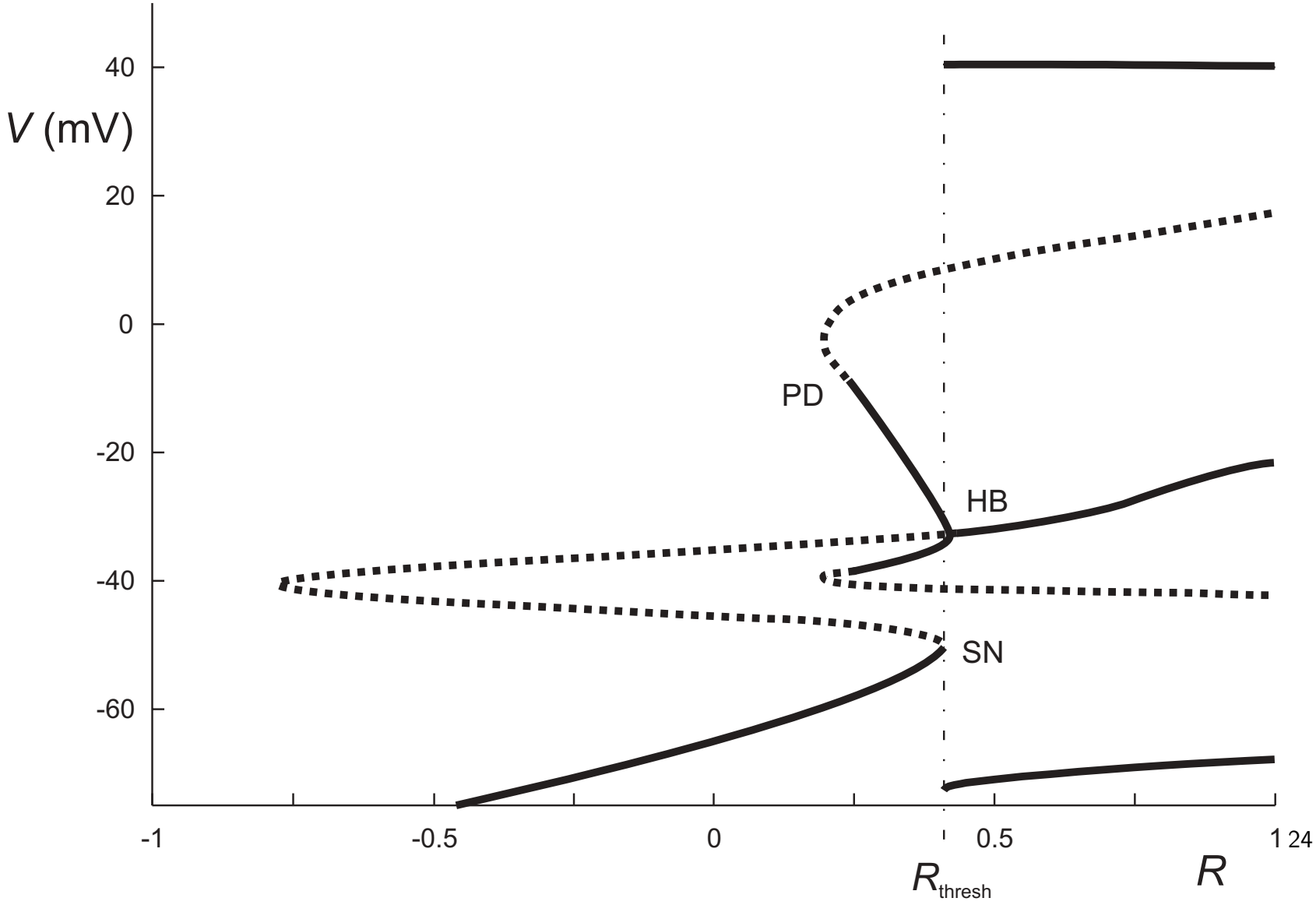


Analysis: the $Fast/Slow$ reduction

To analyze the phasic model – first split into *fast* and *slow* components

- ***fast***: the spiking currents – I_{Na}, I_{Ca}, I_K, I_A, I_c
- ***slow***: the plateau oscillation – $[\mathrm{Ca}^{2+}]_i$ and D

Spiking currents (I_{spike}) pass through saddle-node bifurcation as plateau amplitude increased:



Dissociation of $SLOW$ from $FAST$ nontrivial:

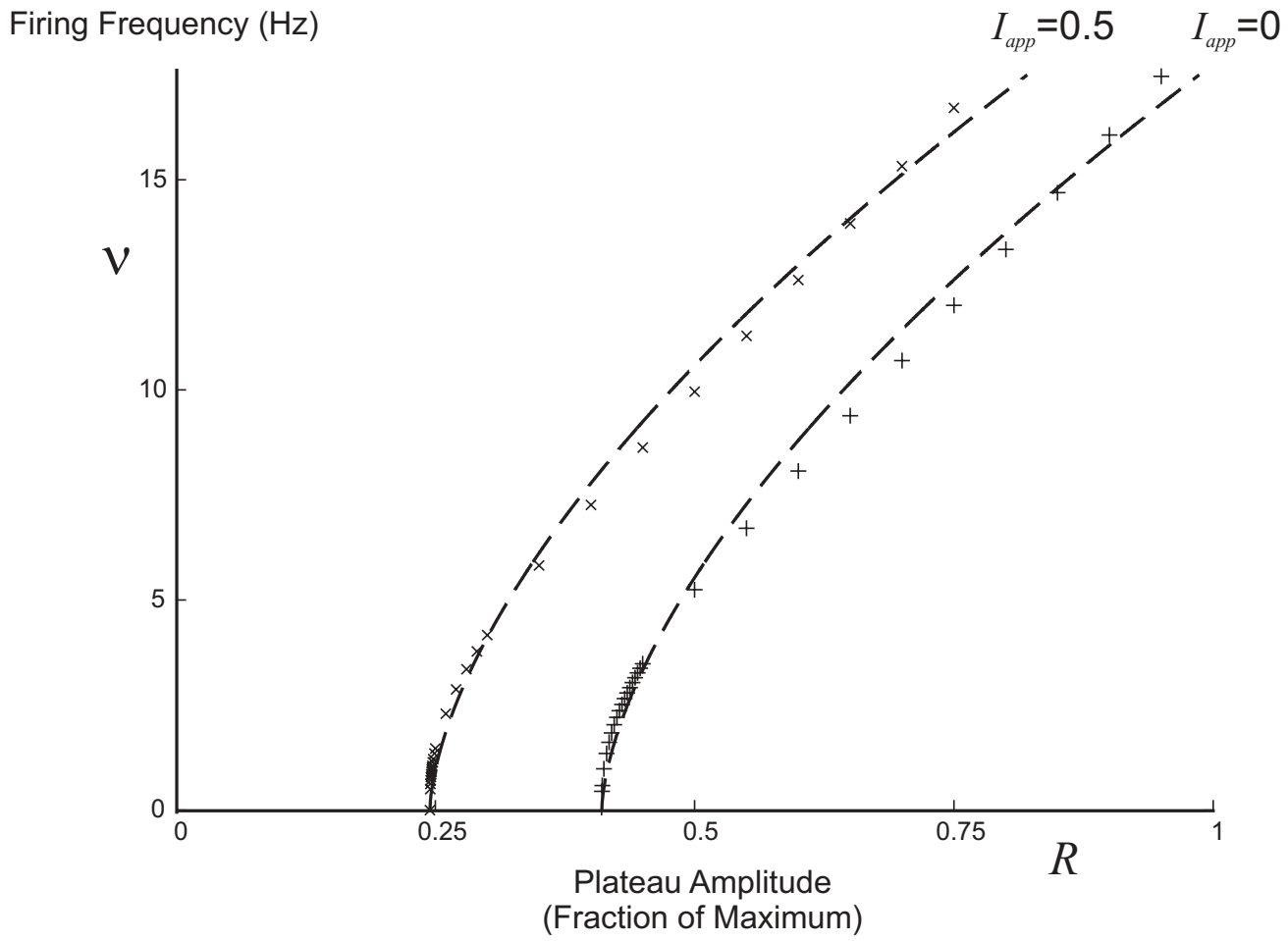
...the two subsystems are not autonomous

Instead write *SLOW* as a firing rate model and decouple subsystems with this *ansatz*

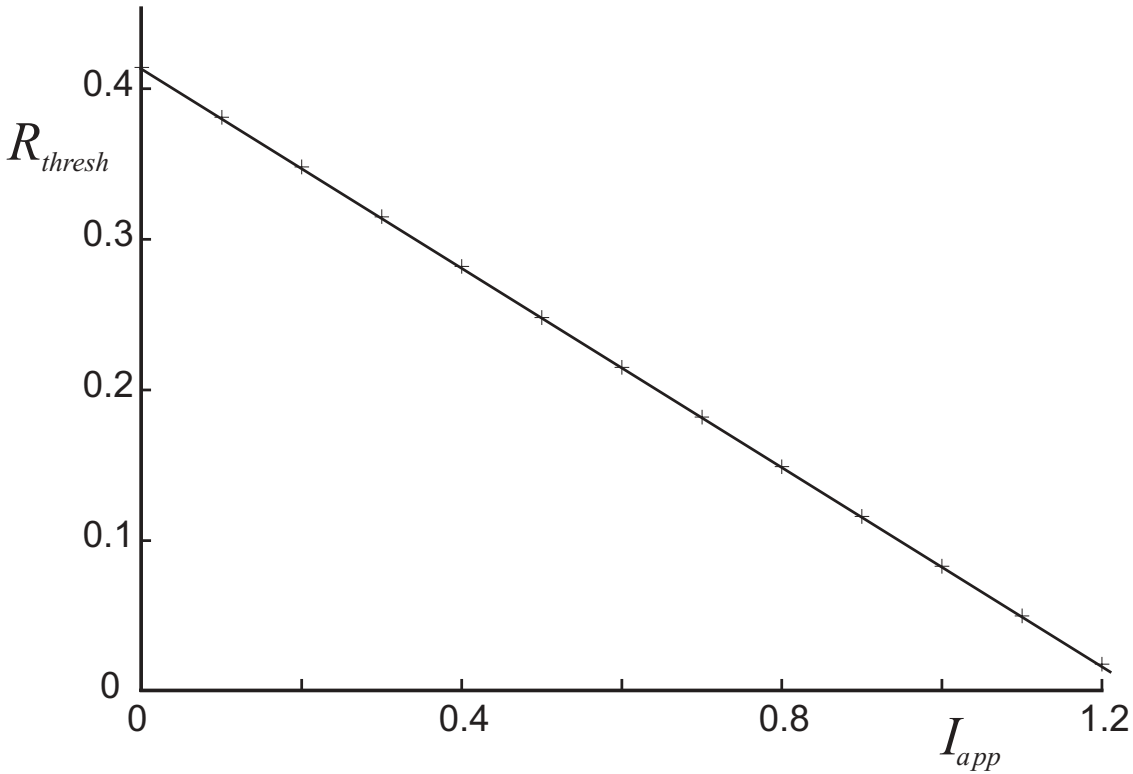
$$\begin{aligned} \frac{d}{dt}C &= \nu(R)\Delta_{Ca} - \frac{1}{\tau_{Ca}}(C - C_r) \\ \frac{d}{dt}D &= \nu(R)\Delta_D - \frac{D}{\tau_D} \end{aligned}$$

Empirically ν can be fit to

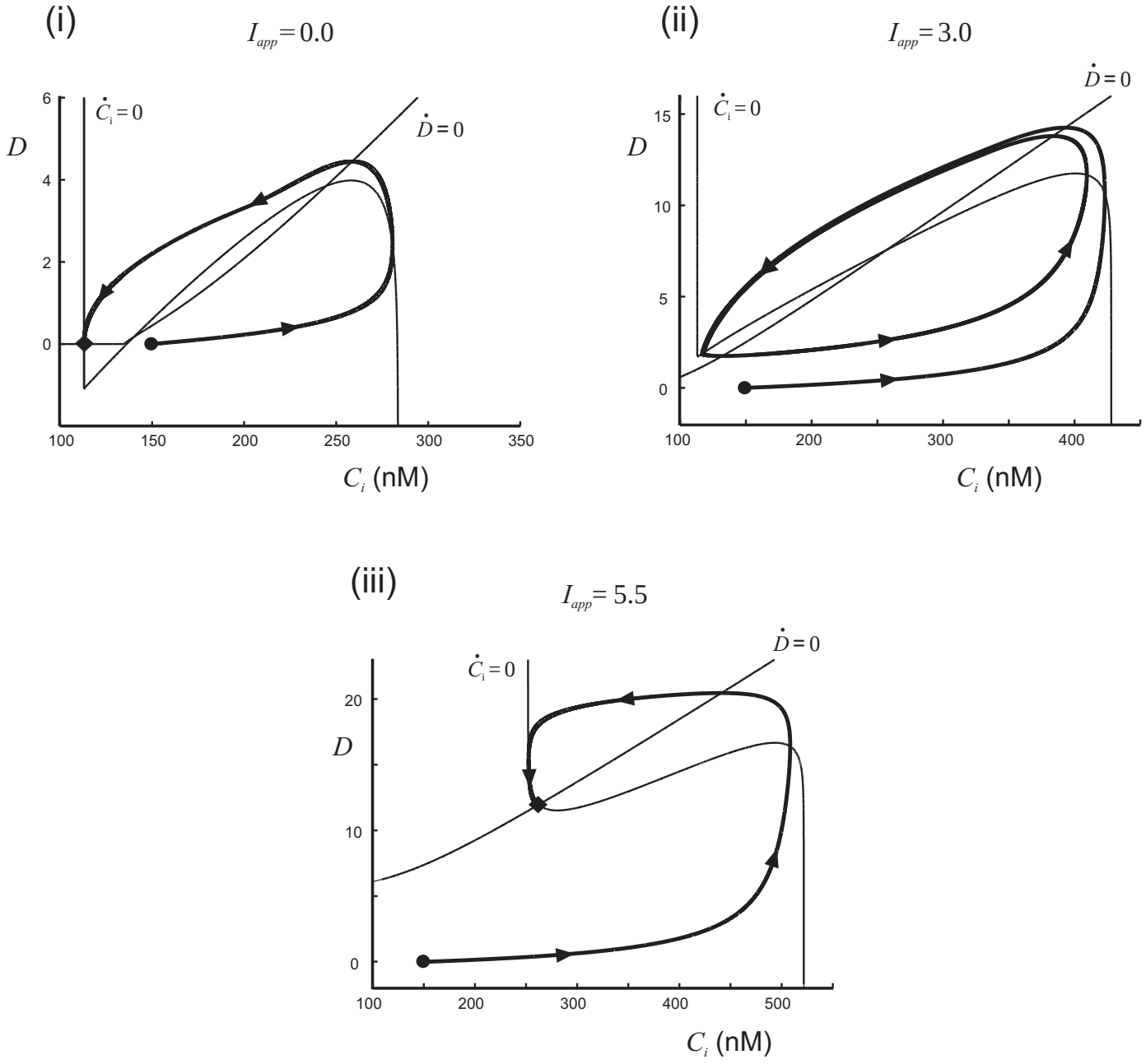
$$\nu = \begin{cases} 0 & R \leq R_{thresh} \\ \Gamma \left(R - R_{thresh} \right)^{\gamma} & R > R_{thresh} \end{cases}$$



and R_{thresh} is a linear function of I_{osm}



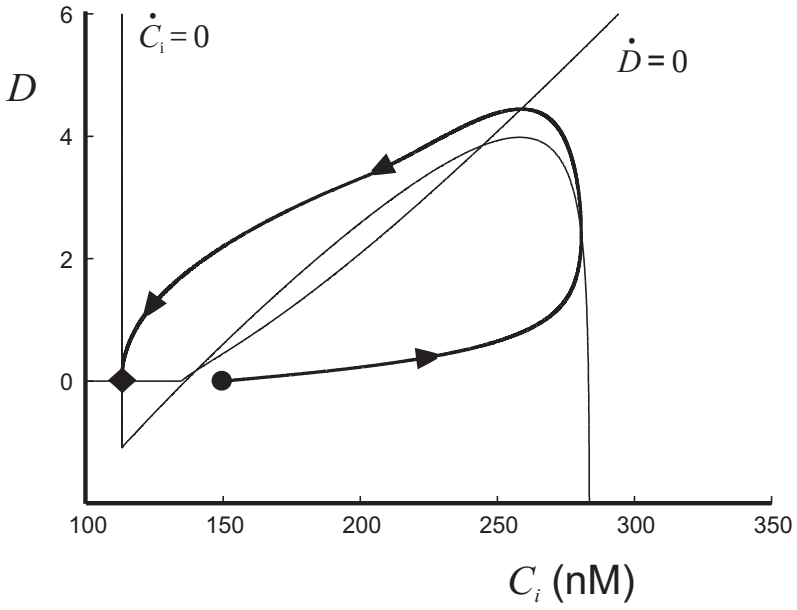
Nullclines

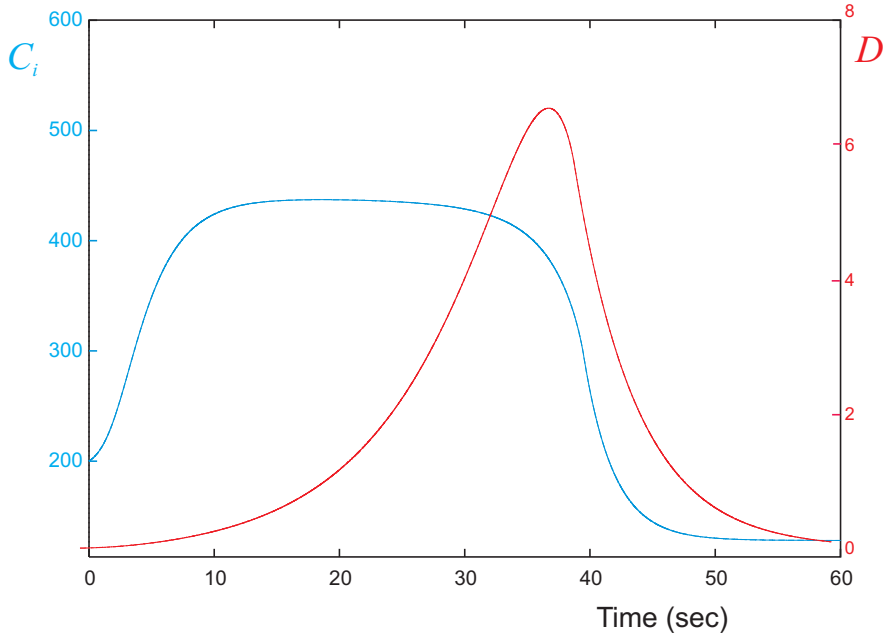

(i)
$I_{app} = 0.0$
$\dot{C}_i = 0$
$\dot{D} = 0$
D
6
4
2
0
100
150
200
250
300
350
C_i (nM)
(ii)
$I_{app} = 3.0$
$\dot{D} = 0$
$\dot{C}_i = 0$
D
15
10
5
0
100
200
300
400
C_i (nM)
(iii)
$I_{app} = 5.5$
$\dot{D} = 0$
$\dot{C}_i = 0$
20
D
10
0
100
200
300
400
500
C_i (nM)

Sub-threshold behaviour

Excitable Bursting – $I_{app} = 0$

- Stable fixed point at $D = 0$ and $[\mathrm{Ca}^{2+}]_i = [\mathrm{Ca}^{2+}]_{rest}$.
- System is excitable – single oscillations can be evoked by moving the system above threshold ($\Delta \mathrm{Ca}^{2+} > 30\mathrm{nM}$).

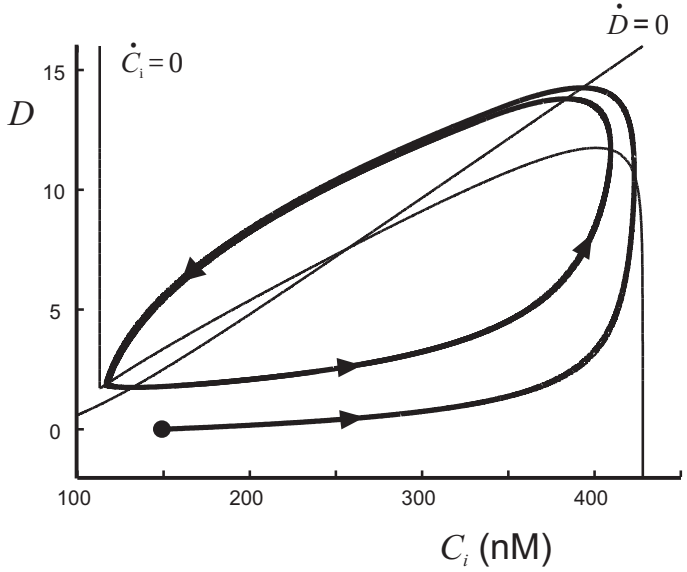


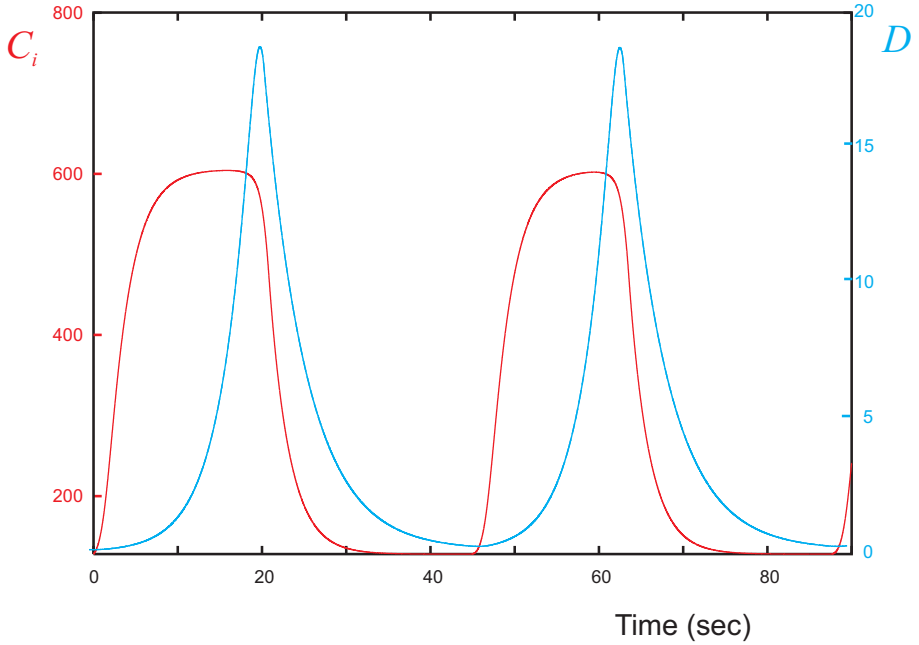


- Single oscillations are equivalent to evoked bursts in the full model.
- Threshold is close to the calcium influx due to 3 spikes.

Super-threshold behaviour

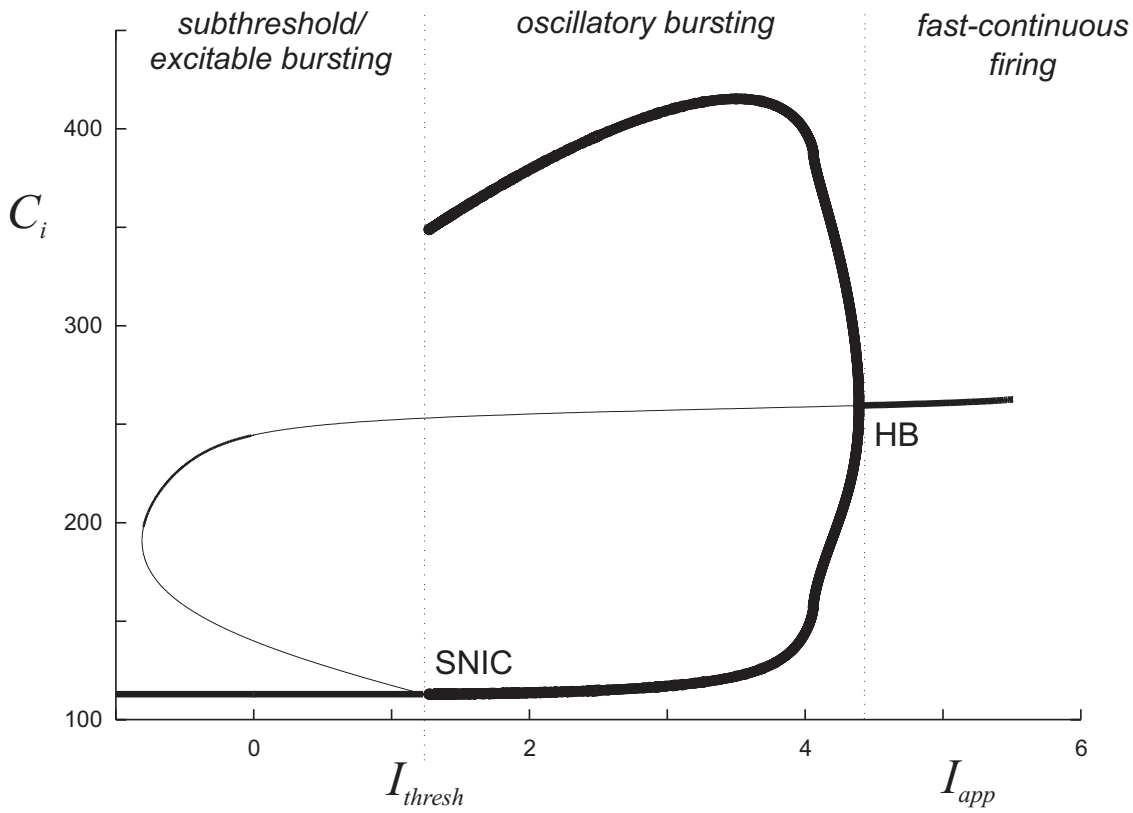
If the applied current (I_{app}) is increased above threshold, then the fixed point loses stability and the system starts to oscillate – phasic activity.





Firing transitions

- stable steady state $\Rrightarrow$ phasic oscillation:
  slow irregular $\Rrightarrow$ *phasic* $\Rrightarrow$ **saddle-node bifurcation**
- phasic oscillation $\Rrightarrow$ stable steady state:
  phasic $\Rrightarrow$ *fast continuous* $\Rrightarrow$ **Hopf Bifurcation**



Conclusions

We have constructed the first qualitative and quantitative model of the electrical activity of vasopressin MNC's

We propose that phasic activity must be driven by an auto-regulatory mechanism, and that dynorphin/κ-opioid receptor secretion is a likely candidate for this mechanism.

Our model reproduces:

- single spikes, basal firing and the fine structure of bursts
- the sequence of firing patterns observed during physiological stress
- (the transient discharge that occurs during sudden stress)

We have also shown that the cells have both excitable and phasic bursting modes: possibly explaining the difference between *in vivo* and *in vitro* recordings.

Collaborators

Theory

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Joseph Callaway (calcium imaging)
Ryoichi Teruyama (electrophysiology)
Talent Shevchenko (electrophysiology)
Chunyan Li (electrophysiology)